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| 09/990,436 | 11/14/2001 | Avi J. Ashkenazi | P2730P1C14 | 2379 |
| 35489 | 7590 | 09/16/2004 | EXAMINER | |
| HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CO 94025-3506 | | | KEMMERER, ELIZABETH | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1646 | |

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/990,436

Applicant(s)

ASHKENAZI ET AL.

Examiner

Elizabeth C. Kemmerer, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 119-123 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 119-123 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 6/25/2004.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment received 25 June 2004 has been entered in full. The Ashkenazi and Polakis declarations accompanying the response are also entered in full. Claims 1-118 and 124 are canceled. Claims 119-123 are under examination

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to the specification regarding hyperlinks as set forth at p. 2 of the previous Office Action (mailed 25 February 2004) is *withdrawn* in view of the amendments to the specification removing the same (amendment of 25 June 2004).

The rejection of claims 119 and 124 under 35 U.S.C. § 112, second paragraph, as set forth at p. 7 of the previous Office Action (mailed 25 February 2004) is *withdrawn* in view of the canceled claim 124 (amendment of 25 June 2004).

The rejection of claims 119 and 124 under 35 U.S.C. § 102(b) as being anticipated by Rolls et al. (1999) as set forth at p. 8 of the previous Office Action (mailed 25 February 2004) is *withdrawn* in view of Applicant's arguments (amendment of 25 June 2004) concerning priority date. The priority date of the instant application is acknowledged to be that of provisional application 60/113,296, filed 22 December 1998.

The rejection of claims 120-123 under 35 U.S.C. § 103(a) as being unpatentable over Rolls et al. in view of De Boer as set forth at pp. 8-10 of the previous Office Action

(mailed 25 February 2004) is *withdrawn* in view of Applicant's arguments (amendment of 25 June 2004) concerning priority date. The priority date of the instant application is acknowledged to be that of provisional application 60/113,296, filed 22 December 1998.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 119-123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The bases for these rejections is set forth at pp. 2-7 of the previous Office Action (mailed 25 February 2004).

Applicant's arguments (submitted with the amendment of 25 June 2004) have been fully considered but are not found to be persuasive for the following reasons. The Ashkenazi and Polakis declarations under 37 CFR 1.132 filed 25 June 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§101 and 112, first paragraph as set forth in the last Office action for the following reasons.

Applicant reviews the evidentiary standard regarding the legal presumption of utility. Applicant argues that the USPTO has not met its burden of overcoming the presumption of the truth of an asserted utility. This has been fully considered but is not

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found to be persuasive. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Furthermore, the rejection does not question the presumption of truth, or credibility, of the asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed antibodies are credible and specific. However, they are not substantial. The data set forth in the specification are preliminary at best. As the courts have discussed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966), an asserted utility must exist in currently available form. The specification indicates that the PRO1112 gene is amplified in certain cancers. However, the literature reports that gene amplification does not necessarily result in increased expression at the mRNA and protein levels. See Pennica et al., Konopka et al., Haynes et al., cited in the previous Office Action.

Applicant urges that the USPTO has not made a *prima facie* case of lack of utility, in that Pennica et al. does not establish a lack of correlation between gene amplification and mRNA expression, and that Konopka et al. is limited to the *abl* gene, which is not recited in the claims. Applicant takes issue with the conclusion that increased copy number may not result in increased protein expression, urging that the standard is not absolute certainty. Applicant argues that the WISP-2 or *abl* genes may be discrepancies. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. This has been fully considered but is not found to be persuasive. Regarding Pennica et al., the WISP-2 gene was still amplified as it was part of the amplicon tested. Furthermore, Pennica et al. used a WISP-2 specific probe

to test for amplification. Although Pennica et al. raise a question regarding the mechanism of the amplification, it is not relevant to the issue at hand since the WISP-2 gene was amplified without a corresponding increase in gene expression. Konopka et al. is relevant in spite of its being directed to a different gene, since it provides an example of an instance wherein a gene is amplified in a tumor whereas there is no corresponding increase in protein expression. The examiner agrees with Applicant's statement that absolute certainty is not the legal standard for utility. However, once again, the credibility of the assertion of utility is not questioned. The asserted utility is not substantial. The literature evidences that gene amplification does not reliably correlate with increased mRNA or protein expression. Therefore, further research would be required by the skilled artisan to determine if the disclosed results regarding a gene amplification event in tumors is also reflected at the mRNA and protein levels. The gene amplification data are preliminary with respect to whether or not the claimed antibodies can be used as a cancer diagnostic. Since the asserted utility that the claimed antibodies can be used as cancer diagnostics is not in currently available form, the asserted utility is not substantial.

Applicant argues that the Haynes et al. publication does not support the rejection. Applicant characterizes Haynes et al. as teaching that there is a general trend but no strong correlation between protein expression level and transcript level. Applicant criticizes Haynes et al. for being directed to a study of yeast proteins. Applicant further characterizes Haynes et al.'s conclusions as showing that there is a positive correlation between transcript and protein for most of the 80 yeast proteins studied, but the

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correlation is not linear and thus one cannot accurately predict protein levels from mRNA levels. Applicant stresses that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and protein. Applicant concludes that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and protein levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO1112. There is no evidence regarding whether or not the PRO1112 **mRNA** or **protein** levels are also increased in these tumor samples. Since the instant claims are directed to PRO1112 **antibody**, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and protein levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Konopka et al. was cited as evidence showing lack of correlation between gene amplification and increased protein levels. Haynes et al. was cited as providing evidence that protein levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO1112 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or

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protein levels. One skilled in the art would do further research to determine whether or not the PRO1112 protein levels increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966), in which the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded protein. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA

levels. This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and protein levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and protein levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1112 in the instant specification. That is, it is not clear whether or not PRO1112 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Protein levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed proteins. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate protein levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form.

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Accordingly, the specification's assertions that the claimed PRO1112 antibodies have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen proteins have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in protein levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1112 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims ¹¹⁹⁻¹²³~~58-65 and 66-70~~ based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels. Furthermore, the declaration does not provide data such that the examiner can independently draw

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conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicant argues that even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Specifically, Applicant refers to the Ashkenazi declaration filed under 37 CFR § 1.132 with the amendment. The declaration and arguments assert that, even when amplification of a gene in a tumor does not correlate with an increase in protein expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-

expression would also be useful; unfortunately, there is no evidence as to whether the gene products (such as the protein) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not present in currently available form, and is not substantial.

Applicant provides evidence in the form of a publication by Hanna et al., attached to the amendment. Applicant urges that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with protein over-expression, and thus the level of protein expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed proteins is not in currently available form, the asserted utility is not substantial.

For all of these reasons, the rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

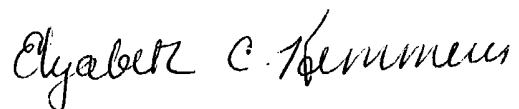
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK



ELIZABETH KEMMERER
PRIMARY EXAMINER